REMARKS

Claims 1-13 and 19-23 are in the application. Claims 15, 16, 18 and 23 are withdrawn from consideration by the Examiner. Claims 1, 11-13, 18 and 22 are amended. Support for the amendment lies in the specification on page 7, lines 21 – 34. No new matter is believed added.

IDS/1449 Forms

The Examiner has attached with the Office Action, Applicants previously submitted 1449 forms. However, only Applicants 1449 forms submitted with the first "Information Disclosure Statement" (submitted 23 October 2008) has the accompanying PTOL 1449 forms completely signed. The Second IDS/1449 form, labeled as "Second Information Disclosure Statement" (also submitted 23 October 2008) only has the first page signed as being reviewed. Pages 2-5 of these 1449 forms are unsigned. Applicants respectfully request that the Examiner review the appropriate citations and return to Applicant the corresponding signed forms. If the Examiner requires any additional information or submittal by Applicant of new forms, please advise the undersigned at the number indicated below.

Restriction Requirement

Applicants respectfully request clarification with regard to the Examiner's comments on page 2 of the Office Action directed to the claims in the present application.

In summary, the claims of Group I of the October 17, 2008 Restriction Requirement are directed to a compound of Formula (I), in which claim 1 defines a Markush group, and Group III is directed to process claims, which are dependent on claim 1. Applicants respectfully point out that the Examiner may hold process claims withdrawn until the determination of patentable or allowable subject matter for the elected group, at which time rejoinder is possible. Based on the foregoing, as elected subject matter for examination on the merits is directed to a product (i.e., compound), Applicants now reserve the right to request rejoinder of commensurate in scope non-elected subject matter or inventions (i.e., such as corresponding treatment methods, pharmaceutical compositions and processes) upon the determination of allowable subject matter (*In re*

Ochiai, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996); also see MPEP § 821.04 (b)).

Moreover, in the January 7, 2009 Office Action, the Examiner indicates that previously presented new claim 23 is withdrawn from consideration. Applicants respectfully disagree with the withdrawal of claim 23.

In particular, pending claim 23, which recites compound species that fall within the scope of claim 1 are properly included in restriction Group I directed to a compound of Formula (I) (i.e., support for claim 23 is found throughout the originally filed disclosure and in original claim 11 of the originally filed disclosure). As no art has been found to limit the scope of the claim 1, which defines a Markush group, the species defined in claim 23 should be examined as part of restriction Group I, directed to compounds of Formula (I).
Applicants request that the Examiner reconsider including claim 23 in restriction Group I for examination on the merits.

For the record, Applicants point out that as claims 14 and 17 were cancelled in the above-identified application, only claims 15 and 16 are to be considered as corresponding to non-elected Group II.

Based upon the foregoing, Applicants respectfully request that the Examiner consider above comments and remove the Finality of the Restriction Requirement as proper.

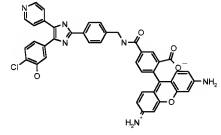
Priority
The present application is the §371 national stage entry of a Great Britain provisional application. While a reading of 37 CFR §1.78(a) and 35 CFR §365(c) is not believed to require such an amendment to the specification, Applicants have done so accordingly per the Examiners request.

Rejection under 35 USC §112, First Paragraph, Scope of Enablement

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as being enabling for the compounds of Formula (I), but not being enabling for "use of the same". Applicants respectfully traverse this rejection

The compounds claimed herein are all p38 kinase inhibitors. The specification clearly contains sufficient information on how to "use". See pages 22, lines 1 to 42 – page 32, lines 1 -11. In the Specification, pages 107, lines 35 to 41 – pages 110, lines 1 – 23 clearly teach suitable assays to determine activity. Contrary to the Examiner's assertion that the "Neither p38 kinase inhibition nor cessation of cell proliferation with the instantly claimed compounds has been demonstrated." (see Office Action Page 5, lines 5-6), activity for actual examples has been demonstrated therein. See page 110, lines 21 and 22 of the Specification. In fact, it should be noted that here is no requirement to provide actual data in the specification.

The Examiner comments that the "experimental protocols only mention the following compound:



and details a procedure on how to measure p38 kinase inhibition and how to determine whether cell proliferation has been halted". (See Office Action, Page 5, 1rst ¶).

The Examiner is correct that the compound above is mentioned therein. The compound is the fluorescent ligand used in the assay. It is not a compound of Formula (I), but used with a variable concentration of a compound of Formula (I) along with the p38 kinase enzyme. The specification actually discloses three variations of the Fluorescence kinase binding assay, which basically vary little on the volume of the testing liquid used.

The compounds of the Examples "were tested in at least one of these assays and had either IC_{50} values of <10 μM or pKi values of >6", as is shown on page 110, lines 22 and 23, as noted above. It should be noted that this is an art recognized assay for determining inhibitory activity of a compound against p38 kinase.

With respect to the state of the art at the time the application was filed, the signaling pathway of p38 kinase had been extensively studied. Applicants have previously provided on their IDS and 1449 forms additional information on the utility of p38 inhibitors for treatment of a wide range of diseases, including inflammation. It is well established in the art that there is a correlation of p38 inhibition and its affect on the pro-inflammatory cytokine cascade. Consequently, Applicants believe that they have provided sufficient grounds of enablement for the compounds of Formula (I) as described herein.

In particular the Examiner's attention is drawn to a previously submitted article on signalling cascades in inflammatory diseases (see Herlaar, E. et al., Molecular Med Today (1999), Vol. 5, 439-447). This article and other previously submitted articles on p38 kinase inhibitors detail the linkage to a number of acute and chronic inflammatory diseases, such as RA, osteoarthritis, inflammatory bowel disease, toxic shock syndrome, septic shock, asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and osteoporosis. The skilled artisan would also be aware of the many more articles and work in the field which describes the role of pro-inflammatory cytokines in the diseases enumerated herein.

Applicants respectfully submit that the originally filed disclosure provides sufficient information on how to formulate, how to dose, and how to administer the compounds of Formula (I). Based on this, Applicants maintain that the specification is sufficiently enabled and would not require undue experimentation to practice the invention.

In the interests of advancing prosecution the method of use claims have been cancelled. Applicants reserve their right to continue prosecution on all cancelled subject matter in subsequent divisional or continuation application in accordance with U.S. Patent Practice.

In view of these remarks and amendments reconsideration and withdrawal of the rejection to the claims is respectfully requested.

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as being enabling for the compounds of Formula (I), but does not "reasonably provide enablement for derivatives of the compounds of Formula (I)". Applicants respectfully traverse this rejection.

As the term "pharmaceutically acceptable derivative" is defined in the specification on page 7, lines 21 to 31, the intended meaning of this term is clear based on the originally filed disclosure. In light of this, the skilled artisan would readily understand how to make a salt, solvate, ester, or a carbamate and/or phosphate ester of a compound of Formula (I).

However, in order to advance prosecution on the merits, Applicants have amended claims 1, 11-13, 18 and 22 to recite the phrase "pharmaceutically acceptable salt" as fully supported by the originally filed disclosure.

Rejection under 35 USC §112, First Paragraph, Written Description

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner comments that the specification discloses "chemicals, such as compounds of formula I" which meet the written description and enablement for under 35 USC §112, first paragraph. (See Office Action, Page 12, lines 1-2, 2nd ¶). The Examiner then comments that claims 1-2, 4-6,9 and 18-20 are directed to encompass derivatives which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these derivatives meet the written description provision due to "lacking chemical structural information for what they are".

Applicants are unclear as to what subject matter appears in claims 1-2, 4-6,9 and 18-20 that is not present in claims 3, 7, 8, 9-13, 19, 21 and 22? As noted above under the enablement rejection, the term "pharmaceutically acceptable derivative" is defined in the specification on page 7, lines 21 to 31, and reproduced below:

> "As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the

extent of teaching such derivatives. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and esters. "

The intended meaning of this term is clear based on the originally filed disclosure. In light of this teaching, the skilled artisan would readily understand how to make a salt, solvate, ester, or a carbamate and/or phosphate ester of a compound of Formula (I).

If the Examiner is commenting on a failure to meet the written description requirement of another term in Claims 1, 11, 12, 18 and 22 clarification is respectfully requested.

As Applicants have amended claims 1, 11-13, 18 and 22 to recite the phrase "pharmaceutically acceptable salt" as fully supported by the originally filed disclosure in place of "pharmaceutically acceptable derivative" (as supported on page 7, lines 14-20 and 32-43; and on page 8 lines 1-18) this rejection is believed to be rendered moot.

In view of these remarks and amendments reconsideration and withdrawal of the rejection to the claims is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper, the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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